REMARKS

Claims 56-116 are currently pending. In the Final Office Action mailed June 13, 2006, the Examiner has raised several issues, which are set forth by number in the order they are addressed herein:

1) Claims 56-116 stand rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement;
2) Claims 56-116 stand rejected under 35 U.S.C. 112, first paragraph, as allegedly lacking enablement;
3) Claims 56-66, 68-83, 85-99 and 101-115 stand rejected under 35 U.S.C. 102(b) as allegedly anticipated by Pumpens (Intervirology, 38:63-74, 1995);
4) Claims 56-116 stand rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Pumpens and Birkett (U.S. Patent No. 6,231,864); and
5) Claims 56-116 stand rejected under the grounds of nonstatutory obviousness-type double patenting as allegedly unpatentable over Claims 25-30 of co-pending Application No. 10/630,070.

Applicants hereby amend Claims 56, 69, 72-74, 76, 81-85, 90 and 102, cancel Claims 71 and 103, and add new Claims 117-124, in order to further the prosecution of the present application and Applicants' business interests, yet without acquiescing to the Examiner's arguments. Applicants reserve the right to prosecute the original, similar, or broader claims in one or more future application(s). The amendments do not introduce new matter. Since new Claims 117-124 are of narrower scope than the amended independent Claims 56, 69, 90 and 102, Applicants respectfully request that the Examiner consider the new claims in the pending Response to Final Office Action.

1) The Amended Claims Meet the Written Description Requirement

The Examiner has rejected Claims 56-116 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement for providing:

> no structural limitations (only cited biological property is an isoelectric point in the range of below 7.0) to the heterologous antigens, no limitations to the insert sites in a hepadnavirus core, and no limitations to the species of hepadnavirus. ... While having written description of a method of making a woodchuck hepatitis

> core antigens (WHcAg) by incorporating with foreign antigens less than 20-mer at the C-terminus of WHcAg identified in the specification tables and/or examples, the instant specification has not provided sufficient written descriptive information about making modified hepadnavirus core antigens by incorporating any foreign peptides/proteins into any position of WHcAg, nor core antigens of other species of the hepadnaviruses, such as those from other rodents, avian, non-human primates, etc. (Final Office Action, page 5).

Although Applicants respectfully disagree with this rejection, Applicants hereby amend Claims 56, 69, 72-74, 76, 81-85, 90 and 102, cancel Claims 71 and 103, and add new Claims 117-124, in order to further the prosecution of the present application and Applicants' business interests, yet without acquiescing to the Examiner's arguments, and while reserving the right to prosecute the original, similar, or broader claims in one or more future application(s). Specifically, Applicants have amended independent Claims 56, 69, 90 and 112, to recite that: 1) said heterologous antigen is 50 or fewer amino acids in length and has an isoelectric point greater than or equal to 7.0; 2) said hepadnavirus core antigen is selected from the group consisting of a woodchuck hepadnavirus core antigen, a ground squirrel hepadnavirus core antigen and a human hepadnavirus core antigen; 3) determining that the isoelectric point of said heterologous antigen encoded by said first nucleic acid is greater than or equal to 7.0, and adding nucleotides that encode an acidic amino acid to said first nucleic acid to reduce said isoelectric point below 7.0; and 4) said combining comprises placing said first and second nucleic acids in operable combination such that said heterologous antigen is expressable within said immunodominant loop or said alpha-helix adjacent to said immunodominant loop. In addition, Applicants have added new dependent Claims 117-124 indicating that some embodiments comprise a heterologous antigen of 26 or fewer, or 20 or fewer amino acids in length. Support for the amendments and new claims can be found throughout the Specification. For instance support for the heterologous antigen limitations of the pending claims can be found in the definition section, as well as in Examples 8, 9 and 15, and in particular Tables 10, 13, 17 and 18 of the application as filed. For example, support for a heterologous antigen of 50 or fewer amino acid residues is provided by the definition of "antigen" as exemplified by "molecules which contain a peptide," and by the definition of "peptide" as encompassing molecules containing from two (2) to about fifty (50) amino acids (Specification, paragraphs [0136-0138]). Similarly, support for a heterologous antigen of 26 or fewer amino acids is provided by the exemplary 26mer HV-2

epitope (SEQ ID NO:71), while support for a heterologous antigen of 20 or fewer amino acids is provided by the exemplary 20mer M epitope (SEQ ID NO:74), which were all successfully inserted into a hepadnavirus core antigen within or adjacent to the immunodominant loop (e.g., and in other embodiments successfully inserted at the natural or an artificial hepadnavirus C-terminus). Likewise, support for the hepadnavirus core antigen limitations of the pending claims can be found in the definitions section (Specification, paragraphs [0120-0123], as well as the description, which provides sequences for wild type woodchuck, ground squirrel and human hepadnavirus cores and numerous sequences for C-terminal modifications of woodchuck, ground squirrel and human hepadnavirus cores (Specification, paragraphs [0180-0190], including Tables 1, 3, and 4, and Figures 40-42).

Thus, the amended claims comprise further structural limitations (e.g., heterologous antigen size and addition of one or more acidic amino acid residues), as well as limitations to insert site (e.g., within or adjacent to the hepadnavirus immunodominant loop), and hepadnavirus species (e.g., woodchuck, ground squirrel and human cores). In addition, Applicants allege that the "isoelectric point greater than or equal to 7.0" limitation is a structural limitation since the pI is a product of the primary amino acid sequence of the heterologous antigen (e.g., the heterologous antigen cannot comprise only acidic and neutral amino acid residues). Applicants respectfully contend that the Specification provides more than sufficient support for the amended claims, and respectfully requests that this rejection be withdrawn.

2) The Amended Claims Are Enabled

The Examiner has rejected Claims 56-116 under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. The Examiner states:

> while being enabling for a method for making a modified recombinant WHcAg by incorporating a foreign antigen less than 20-mer into its C-terminus, does not reasonably provide enablement for a method of making all modified hepadnavirus core antigens by incorporating any peptides/proteins into any positions of any known or unknown species of hepadnavirus core antigens (Final Office Action, page 6).

Although Applicants respectfully disagree with this rejection, Applicants hereby amend Claims 56, 69, 72-74, 76, 81-85, 90 and 102, cancel Claims 71 and 103, and add new Claims 117-124, as

described above in Section 1. Applicants respectfully assert that the scope of the amended claims is commensurate with the teachings of the experimental examples in light of knowledge of one skilled in the art. To begin with, Pumpens, which has been cited by the Examiner as prior art, teaches that the "upper limit for N-terminal (table 1) and internal (table 2) insertions lies in the range of about 50 amino acid residues (Pumpens, page 69, right column, first full paragraph). Specifically, Table 2 of Pumpens discloses the successful insertions of 11 heterologous antigens of greater than 20 amino acid residues in length including a 43mer and a 41mer. Moreover as discussed above, Applicants have successfully produced modified WHcAg and HBcAg cores comprising heterologous antigens of 50 amino acids or less, within or adjacent to the immunodominant loop (Specification, Table 18), and have taught methods for producing modified GSHcAg cores comprising heterologous antigens of 50 amino acids or less, within or adjacent to the immunodominant loop. In fact, Applicants were successful in inserting 22 out of 24 exemplary heterologous antigens tested into woodchuck hepadnavirus cores (Specification, Table 10). Accordingly, Applicants respectfully request that this rejection be withdrawn.

3 & 4) The Amended Claims Are Novel and Nonobvious over Pumpens and Birkett

The Examiner has rejected Claims 56-66, 68-83, 85-99 and 101-115 under 35 U.S.C. 102(b) as allegedly anticipated by Pumpens (Intervirology, 38:63-74, 1995), and has rejected Claims 56-116 under 35 U.S.C. 103(a) as allegedly unpatentable over Pumpens and Birkett (U.S. Patent No. 6,231,864). The Examiner states that:

> a species will anticipate a claim to a genus. "A generic claim cannot be allowed to an applicant if the prior art discloses a species falling within the claimed genus.
>
> Since HBcAg is a species of [hepadnavirus], the method of making a recombinant HBsAg containing a foreign peptide as taught by Pumpens will anticipate a method of making a recombinant hepadnavirus core antigen (genus) ... Pumpens discloses the epitopes incorporated in HBcAg particles through inherency. As shown in Table 17 of the instant specification, Applicant has demonstrated that positively charged inserts (e.g., pI equal to or greater than 7.0) appear to adversely effected assembly of hybrid WHcAg or HBcAg particles. In other words, the recombinant HBcAg disclosed by Pumpens would have a property of isoelectric point less than 7.0 because they can form stable [VLPs]. Thus, the epitopes incorporated in HBcAg particles inherently have isoelectric points less than 7.0 (Final Office Action, pages 10 and 11).

Applicants respectfully disagree with this rejection. Applicants contend the Examiner's logic in concluding that the epitopes of Pumpens must inherently possess a pI of less than 7.0 because they form stable particles is flawed. In fact, Applicants teach that the hybrid hepadnavirus cores containing a SEB epitope (SEQ ID NO:78) with a pI of 8.63 assemble, albeit less well than hybrid particles containing heterologous antigens with an acidic pI (Specification, Table 17). Thus, Pumpens has not been shown to teach a species of the genus as currently claimed directly or through inherency.

Nonetheless Applicants have amended Claims 56, 69, 72-74, 76, 81-85, 90 and 102, canceled Claims 71 and 103, and added new Claims 117-124, as described above in Section 1. The amended claims are not anticipated by or obvious over Pumpens and Birkett, because neither Pumpens nor Birkett teach or suggest all of the limitations of the amended claims. In the first place neither reference teaches or suggests "determining that the isoelectric point of said heterologous antigen encoded by said first nucleic acid is greater than or equal to 7.0, and adding nucleotides that encode an acidic amino acid to said first nucleic acid to reduce said isoelectric point below 7.0" as required by independent Claims 56, 69, 90 and 102. Specifically, Pumpens and Birkett DO NOT teach *determining the pI of the heterologous antigens*, let alone the utility of *adding nucleotides to reduce the pI of the heterologous antigen.* In fact, Table 2 of Pumpens does not provide the sequence of the heterologous antigens or sufficient detail regarding the cloning of the hybrid particles containing internally inserted epitopes. Tables 1 and 3 of Pumpens are irrelevant since they list hybrid particles containing N-terminal and C-terminal inserts, respectively, while the amended claims are directed to hybrid particles containing inserts within or adjacent to the immunodominant loop.

Additionally, neither Pumpens nor Birkett teach or suggest that adding nucleotides to reduce the pI of the heterologous antigen for *"rescuing" assembly* of a hybrid hepadnavirus particle as required by Claim 57 and 70. Similarly, Pumpens and Birkett do not teach adding nucleotides to reduce the pI of a heterologous antigen from greater than or equal to 7.0, to *3.0-5.0* as required by Claims 58 and 91. Likewise, it does not follow from the Examiner's inherency argument that Pumpens or Birkett discloses *substitution of a non-acidic amino acid residue or insertion of an acidic amino acid residue* within or adjacent to the heterologous antigen as required by Claims 59-63, 74-80, 92-96, and 106-112. Thus, Pumpens and Birkett do

not anticipate or make obvious either the pending independent claims or the narrower pending dependent claims.

Even though the Examiner has not established a *prima facie* case of obviousness of the invention as currently claimed, Applicants respectfully submit that the Specification as filed provides evidence of unexpected results. In particular, as described in Example 15, Applicants have successfully expressed an HIV-1 heterologous antigen (SEQ ID NO:85) in both modified WHcAg and HBcAg cores (Specification, Table 18). This was accomplished using methods comprising determining that this heterologous antigen of 50 or fewer amino acid resides has a pI greater than or equal to 7.0 (pI ~ 11.3), and adding nucleotides encoding acidic amino acid residues to a nucleic acid encoding the heterologous antigen. This is in contrast to the teachings of PCT/US01/25625 of Birkett, which discloses that the HIV4.1 epitope was not "expressed for reasons unknown" when inserted into HBcAg cores (Specification, footnote to Table 17 citing PCT/US01/25625 = WO 02/13765, IDS reference 14, at pages 100 and 101).

As the combination of references does not teach or suggest all of the limitations of the pending claims and as Applicants have provided evidence of nonobviousness in the Specification, Applicants respectfully request that these prior art rejections be withdrawn.

5) There is No Double-Patenting

The Examiner has rejected Claims 56-116 under the grounds of nonstatutory obviousness-type double patenting as allegedly unpatentable over Claims 25-30 of co-pending Application No. 10/630,070. Applicants have canceled Claims 25-30 of co-pending Application No. 10/630,070 in a paper filed on August 8, 2006. As such, Applicants respectfully request that this rejection be withdrawn.

PATENT
Attorney Docket No. **VACCINE-07971**

CONCLUSION

Applicants believe the arguments and amendments set forth above traverse the Examiner's rejections and place the application in a condition for allowance and such action is earnestly solicited. If, however, any unresolved issues remain, the Examiner is cordially invited to contact the undersigned so that these matters can be addressed in an expeditious manner.

Dated: August 9, 2006

By: _____

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